Effervescent preparations

The invention relates to a process for producing medicament-containing effervescent preparations with at least partial melting of a preparation component and to effervescent preparations obtainable by this process.

Effervescent preparations such as, for example, effervescent powders or effervescent tablets are a formulation form, for example for active substances with a long absorption time or with a tendency to irritate the gastric mucosa, which is able to mitigate the disadvantageous properties mentioned for the active substances. Medicament-containing effervescent preparations therefore enjoy increasing popularity. They are normally produced in 3 to 4 stages, namely by

a) granulating the effervescent composition consisting of CO_2 donor and CO_2-releasing acidic component,
b) mixing the other components (active substances and other ancillary substances),
c) combining the components obtained from process steps a) and b) and, where appropriate,
d) tabletting the mixture obtained in step c).

Since both the CO_2 donor and the acidic component are relatively unsuitable for direct tabletting, the components of the effervescent composition have in the past been subjected, where appropriate in combination with the active substance, to a granulation process before the tabletting; compare, for example, German Offenlegungsschrift 22 16 072. The stability of the effervescent tablets produced in this way is, however, still unsatisfactory. The additional use of buffer substances and flavourings (which, after all, usually consist of many individual different compounds) in particular results in a sensitivity to water which leads, on storage, to discoloration, distension and degradation reactions. To avoid these unwanted reactions, effervescent preparations are often sealed in metal foils. Although this measure extends the shelf life, it is not possible reliably to prevent distension of the metal foil sachets on prolonged storage.

It has now been found, surprisingly, that the stability of medicament-containing effervescent preparations can be increased by a process in which a preparation component is melted.

Sub R2

The invention thus relates to a process for producing medicament-containing effervescent preparations consisting of

A. effervescent composition containing
   (i) CO_2 donor and
   (ii) acidic component,
B. pharmaceutical active substance and
C. ancillary substance,

characterized in that

at least one of the two components A(i), A(ii) and, where appropriate, other effervescent preparation components are dispersed in molten C) sugar and/or sugar alcohol and/or sugar substitute, and the resulting mixture is tabletted where appropriate.

The invention entails dispersing where appropriate one, a plurality or all of the remaining effervescent preparation components in the melt.

A preferred process is characterized in that

- a melt of component A(i) and/or A(ii) and C) fusible sugar and/or sugar alcohol and/or sugar substitute is comminuted during or after the cooling,
- the comminuted product is mixed with active substance B, with component (i) or (ii), which is still missing where appropriate, of the effervescent composition A and, where appropriate, with further ancillary substances C and, where appropriate,
- the resulting mixture is tabletted.

Preferred CO_2 donors A(i) comprise alkali metal and alkaline earth metal carbonates and bicarbonates, especially sodium and potassium carbonates and bicarbonates, and magnesium and calcium carbonates.

Suitable as acidic component A(ii), which liberates carbon dioxide from the CO_2 donor A(i), are all physiologically acceptable acids (so-called "acidulants"), which are strong enough to liberate carbon dioxide from component A(i); such acids have a first equilibrium exponent pKa of from 1 to 7, preferably 2 to 6 (at 25°C). Preferred acidic components A(i) comprise ascorbic acid and polybasic carboxylic acids

having 3 to 8, preferably 4 to 6, C atoms and 2 to 4 carboxyl groups per molecule, such as, for example, vitamin C, malic acid, citric acid, tartaric acid and mixtures thereof.

Sub B3

Suitable pharmaceutical active substances C comprise
analgesics such as ibuprofen, ketoprofen, paracetamol, acetylsalicylic acid, COX_2 inhibitors such as nimesulide, meloxicam, naproxen, propyphenazone, metamizole,
antacids such as hydrotalcite, magaldrate, calcium carbonate,
antiasthmatics/bronchospasmolytics such as salbutamol, tulobuterol, terbutaline, cromoglicic acid, ketotifen, theophylline,
antibiotics such as quinolones, tetracyclines, cephalosporins, penicillins, macrolides, sulphonamides, polypeptides,
phychopharmaceuticals such as benzodiazepines, haloperidol, amitryptyline, carbamazepine,
antirheumatics such as phenylbutazone, indometacin, diclofenac, piroxicam,
antidiabetics such as metformin, glibenclamide, acarbose, glisoxepide,
antiallergics/antihistamines such as astemizole, terfenadine, loratadine, clemastine, bamipine, cetirizine,
antihypotensives such as etilefrine, norfenefrine, dihydroergotamine mesilate,
antitussives such as codeine, dextromethorphan, clobutinol, dropropizine,
antihypertensives such as beta blockers such as propranolol, atenolol, metoprolol, prazosin,
antihypertensives such as calcium channel blockers such as nifedipine, nitrendipine, diltiazem, verapamil, felodipine, nimodipine,
laxatives such as sodium picosulphate, lactulose, lactitol,
mucolytics/expectorants such as ambroxol, bromhexine, guaifenesin, acetylcysteine, carbocisteine,
H2 blockers such as ranitidine, famotidine, pirenzepine,
local anaesthetics such as benzocaine, lidocaine, procaine,
antiemetics/prokinetics such as metoclopramide, domperidone, meclozine, dimenhydrinate,
lipid lowering agents such as fenofibrate, bezafibrate, pravastatin, fluvastatin,
agents effective for migraine, such as caffeine, dihydroergotamine, ergotamine, sumatriptan, pizotifen,
sympathomimetics such as pseudoephedrine, pholedrine,
vitamins and minerals.

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The ancillary substances C, which should melt at least partially in the process according to the invention, have, as single substance and/or in mixtures, preferably melting points of from 30 to 200, preferably from 40 to 160°C. Preferred ancillary substances of this type are soluble in water, that is to say they generally have a solubility in water of at least 10, preferably at least 30, and, in particular, at least 40 g/100 ml of water at 20°C.

Fusible sugars C comprise, for example, monosaccharides such as glucose, mannose, galactose, arabinose, xylose, ribose and disaccharides such as sucrose, lactose, maltose. Sugar alcohols C preferred for the invention comprise xylitol, mannitol, sorbitol, isomalt, lactitol, erythritol, threitol, ribitol, arabitol and dulcitol. Preferred sugar alcohols of this type are described, for example, in EP-B 435 450. The term "sugar substitutes" for the purpose of the invention does not include sugar alcohols. Preferred sugar substitutes C comprise acesulfame, aspartame, saccharin, sodium cyclamate.

Further ancillary substances C comprise flavourings, sweeteners, lubricants, flow regulators, disintegrants and bulking agents such as, for example, starch and starch derivatives, cellulose and cellulose derivatives, polyethylenes.

The effervescent preparations obtainable according to the invention may contain the components in a wide variety of ratios of amounts; preferred effervescent preparations contain (in each case in parts by weight)

A: 5 to 95, preferably 10 to 80,
B: 5 to 95, preferably 40 to 60,
C: 1 to 60, preferably 15 to 30 (sugar, sugar alcohol, or sugar substitute) and, where appropriate,
1 to 50, preferably 5 to 15 (other ancillary substances).

The effervescent composition A preferably contains
30 to 70% by weight of CO_2 donor and
70 to 30% by weight of acidic component,
in each case based on A.

The melt of effervescent composition A (component) and fusible sugar and/or sugar alcohol and/or sugar substitute C can be prepared, for example, by adding

effervescent composition A (components) to a melt of sugar and/or sugar alcohol and/or sugar substitute C or by melting a mixture of effervescent composition A (components) and sugar and/or sugar alcohol and/or sugar substitute C.

However, the process according to the invention can also be carried out by contacting all components of the effervescent preparation with the molten sugar and/or sugar alcohol and/or sugar substitute for the purpose of dispersion, whether by premixing all components and heating together, or whether by melting sugar and/or sugar alcohol and/or sugar substitute and dispersing the remaining components (simultaneously or successively) in the melt. It is, of course, possible to use mixed forms of the process variants described.

The melt can be produced in virtually any suitable manner;
Thus, it is possible straightforwardly to use heatable stirred vessels. It is also possible to use a melt-granulation process as described, for example, in WO 92/6679. A preferred process is melt extrusion as described, for example, in EP-A 686 392. It is possible to employ for the extrusion commercially available single screw and twin-screw extruders. It is moreover possible to feed the starting materials to the extrusion via a weigh feeder. The melt temperature can be 30 to 200°C. The pressure can preferably be 2 to 200 bar, depending on the die orifice (preferably 0.5 to 5 mm) and the speed of rotation (preferably 5 to 400 revolutions/minute). The output can vary within wide limits, but is preferably 1 to 100 kg/hour. The extrudates are cooled where appropriate. After the comminution, they can be mixed with active substance B and, where appropriate, further ancillary substances C, and tabletted where appropriate.

Preferably neither water nor an organic solvent which is volatile under the processing conditions is employed in the process according to the invention, that is to say preferably water and solvent are absent from the process. In other words,: the process is precisely not that described in German Offenlegungsschrift 22 16 072 or in
Acta Pharm. Suec., 24, (2), 84, 1987
Drug Dev. Ind. Pharm. 13, (9-11), 1891-1913, 1987
Drug Dev. Ind. Pharm. 14, (13), 1791-98, 1988.

The process according to the invention can be carried out continuously or batchwise.

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In the process according to the invention, component A(i) and/or A(ii) and, where appropriate, further effervescent preparation components are dispersed in the fusible sugar, sugar alcohol or sugar substitute C, that is to say the fusible component C forms a matrix in which A(i) and/or A(ii) and, where appropriate, further effervescent preparation components are embedded.

Thus the invention also relates to effervescent preparations consisting of

A. effervescent composition containing
   (i) CO_2 donor and
   (ii) acidic component,
B. pharmaceutical active substance and
C. ancillary substance,

characterized in that ancillary substance C contains fusible sugar and/or sugar alcohol and/or sugar substitute, and component A(i) and/or A(ii) is dispersed in a matrix of fusible sugar and/or sugar alcohol and/or sugar substitute.

The percentage data in the following examples are based on weight in each case.

Examples

Example 1

Effervescent preparation consisting of separately extruded components A(i) and A(ii)

Extrudate I

Mannitol and sodium bicarbonate are mixed in the ratios indicated in the table. The mixture is processed in a twin-screw extruder (Leistriz Micro 27/40D) at a speed of rotation of 30 rpm and with a die diameter of 1 mm. The dies are arranged around the outer diameter of the screws. Mixing zones and die temperature are at 80°C. The extrudate is cooled on a cooling belt and then comminuted with an oscillating sieve.

Extrudate II

Mannitol, citric acid and sodium citrate are mixed and extruded and further processed as above.

	Extrudate I:	Extrudate II:
Mannitol	60%	60%
Sodium bicarbonate	40%	
Citric acid		6.7%
Sodium citrate		33.3%

Based on a single dose, 125 g of extrudate I and 150 mg of extrudate II are mixed with 500 mg of acetylsalicylic acid, 5 mg of aspartame and 30 mg of orange flavour and packed in a sachet.

Example 2

In analogy to Example 1, extrudate I and extrudate II are extruded at a temperature of 70°C, with a die diameter of 0.8 mm and a speed of rotation of 26 rpm.

	Extrudate I:	Extrudate II:
Xylitol	60%	60%
Sodium bicarbonate	40%	
Citric acid		40%

Based on a single dose, 125 mg of extrudate I and 150 mg of extrudate II are mixed with 500 mg of acetylsalicylic acid, 4 mg of saccharin and 30 mg of mandarin flavour and packed in a sachet.

Example 3

In analogy to Example 2, extrudate I and Extrudate II are extruded at a temperature of 60°C, with a die diameter of 1 mm and a speed of rotation of 35 rpm.

	Extrudate I:	Extrudate II:
Xylitol	30%	30%
Sodium bicarbonate	70%	
Citric acid		70%

Based on a single dose, 125 mg of each of extrudate I and II are mixed with 150 mg of ascorbic acid and 2.5 mg of chlorpheniramine maleate and packed in a sachet.

Example 4

In analogy to Example 2, extrudate I and extrudate II are extruded at a temperature of 60°C, with a die diameter of 2 mm and a speed of rotation of 35 rpm

	Extrudate I:	Extrudate II:
Isomalt	60%	
Xylitol		60%
Potassium bicarbonate	40%	
Ascorbic acid		40%

Based on a single dose, 125 mg of extrudate I and 250 mg of extrudate II are mixed with 500 mg of acetylsalicylic acid, 5 mg of saccharin, 2 mg of aspartame and 30 mg of orange flavour and packed in a sachet.

Example 5

In analogy to Example 1, extrudate I and extrudate II are extruded at a temperature of 60°C, with a die diameter of 1 mm and a speed of rotation of 35 rpm.

	Extrudate I:	Extrudate II:
Mannitol	60%	60%
Sodium bicarbonate	20%	
Calcium carbonate	20%	
Ascorbic acid		40%

Based on a single dose, in each case 1500 mg of extrudate I and 750 mg of extrudate II are mixed with 5 mg of aspartame and 10 mg of redcurrant flavour and packed in a sachet.

Example 6

A formulation with only one extruded component, namely A(ii)

Extrudate II from Example 2	1200 mg
Famotidine	10 mg
Sodium bicarbonate	400 mg
Sodium carbonate	100 mg
Magnesium stearate	20 mg

In analogy to Example 1, only the acid component is extruded, and the alkaline effervescent component and the active substance are mixed therewith. Subsequently, magnesium stearate is mixed in. This mixture is compressed to an effervescent tablet.

Example 7

Joint extrusion of A(i) and A(ii)

Xylitol	60%
Na citrate	14%
Sodium bicarbonate	23%
Citric acid	3%

Production process:

A) Extrusion in analogy to Example 1, or

B) Melt xylitol at about 120°C and meter and stir in the components successively. After cooling, the melt cake is comminuted.

Based on a single dose, in each case 600 mg of the resulting extrudate, 200 mg of acetylcysteine and 10 mg of lemon flavour are mixed. The resulting powder mixture is packed in a sachet.

Example 8

A mixture of 54% xylitol, 6% pseudoephedrine, 14% sodium citrate, 23% sodium bicarbonate and 3% citric acid is extruded in analogy to Example 1. The extrudate is comminuted and packaged.

Stability comparison of ASA-containing effervescent formulations

Determination of the degradation product salicylic acid (SA) after storage in packaging impermeable to water vapour at 25°C for 3 months

	Initial SA content	SA content after 3 months
ASA effervescent granules, flavoured*	0.02%	1.61%
ASA effervescent granules (extruded), flavoured[xx]	0.04%	0.18%
ASA effervescent tablet, flavoured*	0.3%	1.83%
ASA effervescent tablet, unflavoured*	0.17%	0.8%

* Granules are produced by conventional technology (comparative test)

XX According to the invention